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EXAMINER	
REDDIG, PETER J	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/516,558	CHANO ET AL.	
	Examiner	Art Unit	
	Peter J. Reddig	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *1-3,11-16 and 18-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-10 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 January 2005* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/8/05; 1/25/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice to Comply*.

DETAILED ACTION

1. Applicant's election without traverse of Group II claims 4-10 and 17, drawn to a nucleic acid coding for the polypeptide or protein according to claim 1 and the species SEQ ID NO: 3 and SEQ ID NO: 19 in the reply filed on July 26, 2007 is acknowledged.

2. Claims 1-26 are pending.

3. Claims 1-3, 11-16 and 18-26 are hereby withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to a non-elected invention.

4. Due to its presence in the prior art SEQ ID NO: 20 will be rejoined for examination.

5. Claims 4-10 and 17, drawn to a nucleic acid coding for the polypeptide or protein according to claim 1 and the species SEQ ID NO: 3 and SEQ ID NO: 19 and 20 are currently under consideration.

Priority

6. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

It is noted that Examiner has established a priority date of January 30, 2003 for the instant application, 10/516,558, because the priority of the instantly claimed invention is based on Japanese applications 2002-161400 and 2002-214978, which have not been translated and the Examiner is unable to determine the information in the documents.

If Applicant disagrees with any rejection set forth in this action based on examiner's establishment of a priority date, January 30, 2003 for the instantly claimed application serial number 10/516,558, Applicant is invited to submit a proper translation of the priority documents and to point to page and line where support can be found establishing an earlier priority date. If

Applicants choose to file a translation, then the translation must be filed together with a statement that the translation of the certified copy is accurate, see MPEP 201.15.

Specification/Drawings

7. The specification and drawings are objected to for improper disclosure of amino acid sequences without a respective sequence identifier, i.e. SEQ ID NOs: see p. 38, lines 24-26, Fig. 12, and Table 1. Hence, the disclosure fails to comply with the requirements of 37 CFR 1.821 through 1.825. In the absence of a sequence identifier for each sequence, Applicant must provide a computer readable form (CRF) copy of the sequence listing, an initial or substitute paper copy of the sequence listing, as well as any amendment directing its entry into the specification, and a statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 CFR 1.821(e-f) or 1.825(b) or 1.825(d). *Failure to supply the appropriate sequences identification numbers in response to this action will be considered non-responsive.*

8. The disclosure is also objected to because of the following informalities: There is a hyperlink in the specification at p. 31, line 19. Removal of the "http://" will disable the hyperlink and obviate this objection.

Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

9. Claims 4-6, 8, and 10 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claims 4-6, 8, and 10, as written, do not sufficiently

distinguish over the nucleic acids SEQ ID NO: 3, 19, and 20 as they exist naturally because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. *See Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (1980). In order to obviate the instant rejection, the Examiner suggests that the claims should be amended to indicate the hand of the inventor, e.g., by insertion of "isolated" or "purified" provided the support for such an amendment can be identified in the specification as originally filed. See MPEP 2105.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 5, 10, and 17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "hybridizing/hybridize under stringent conditions" in claims 5, 10, and 17 renders the claim indefinite. The term " hybridizing under stringent conditions " is not defined by the claim, the specification provides one non-limiting example of hybridizing under stringent conditions and thus it cannot be determined what hybridizing conditions are encompassed by the claims.

Claim 9, which depends on claim 1, recites the limitation "the recombinant vector containing nucleic acid coding for the polypeptide or protein". There is insufficient antecedent basis for this limitation in the claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claim 17 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Claim 17 is drawn to a pharmaceutical composition for use in treatment of multidrug resistance that is resistance to treatment with anticancer agents, wherein the pharmaceutical composition comprises a nucleic acid coding for the polypeptide or protein of claim 1, SEQ ID NO: 3, or a complementary strand thereof, a recombinant vector containing SEQ ID NO: 3, a transformant that was transformed with the recombinant vector containing SEQ ID NO: 3, or nucleic acid primers set forth in SEQ ID NO: 19 and 20 in the sequence listing which hybridize

under stringent conditions with SEQ ID NO: 3. Given the teaching of the specification as set forth below, the claims are reasonably interpreted to mean that the pharmaceutical compositions are to be used for the treatment of multidrug resistance that is resistance to treatment with anticancer agents by administration of the nucleic acids alone or in a transformant to a patient.

The specification teaches that SEQ ID NO: 3, the human RB1CC1 gene, was identified as a differentially expressed gene in U2 Osteosarcoma cells and MDR-variant induced cells, see Example 1, p. 31 and the sequence listing. The specification teaches that the expression of RB1CC1 inversely correlated with the multidrug resistance gene (MDR1), see Example 3 and Fig.1. The specification teaches that doxorubicin reduced the expression of RB1CC1 and the retinoblastoma (RB1) mRNA and overexpression of MDR1 blocked this down regulation, see Example 5 and Fig. 5. The specification teaches that the expression of RB1CC1 and the RB1 mRNA correlated in six cell lines and leukocytes and in several tissues, see Example 6, 7and Fig. 6, 7. The specification teaches that the introduction of RB1CC1 into cell lines induces the expression of the RB1 gene and activation of the RB1 promoter, see Example 8 and 9 and Fig. 9 and 10. The specification teaches that there is a loss of heterozygosity in the RB1CC1 gene in 5 of 7 primary breast cancer tumors examined, see Example 10 and Fig. 11. The specification teaches that 7 mutations in the RB1CC1 gene were found among 35 primary breast cancer samples analyzed using PCR and sequencing with the primers of the invention, including SEQ ID NO: 19 and 20, see Example 11 and 12, Table 2 and Fig. 12. The specification teaches that the combination of primers set forth in SEQ I D NOs: 19 and 20 in the sequence listing (CC1-S and CC1-AS) were used as primers for amplification of RB1CC, see p.36, lines 15-18.

The specification teaches that MDR resistance to treatment with anticancer agents is a major barrier to the successful treatments of cancer. While current understanding of factors that contribute to origins of MDR is limited, it is considered that P-glycoprotein that is a product of an MDR-associated gene (MDR1 gene) is involved in several cancers. It is also known that in other cancers expression of P-glycoprotein correlates inversely with emergence and metastasis of the cancer. It is considered that these different effects of P-glycoprotein are subject to suppression by different gene products or conduct different interactions. The identification of genes associated with MDR is essential in order to clarify these phenomena, see Background of Invention.

The instant specification provides insufficient guidance and objective evidence to predictably enable one of skill in the art to use the invention as claimed and no nexus has been established between the claimed pharmaceutical compositions and treating multidrug resistance that is resistance to treatment with anticancer agents, which reads on cancer therapeutics, because inferred by and inherent in the recitation of a pharmaceutical composition is the in vivo use thereof for the treatment of disease. Given that the only apparent contemplated use for the pharmaceutical composition is drawn to the use of the claimed invention for the treatment of cancer MDR, it is clear that the claimed invention is for use in the treatment of cancer patients who have developed multidrug resistance.

It is noted however, that the art recognizes the unpredictability of developing novel cancer therapeutics. Given the claimed nucleic acid pharmaceutical, it appears that the claims are drawn to a pharmaceutical composition for (1) immunotherapy of MDR upon expression of the encoded protein and (2) treatment of multidrug resistance by gene therapy and the art recognizes the unpredictability of treating a disease by a method of gene therapy.

As drawn to the art of anti-cancer therapy in general, it is noted that Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models that only 29 have actually been shown to be useful for chemotherapy (p. 1041, see 1st and 2nd para.). Furthermore, Kaiser (Science, 2006, 313, 1370) teaches that 90% of tumor drugs fail in patients, see 3rd col., 2nd to last para.

1) As drawn to anticancer immunotherapy by administration of nucleic acid encoding an antigen, which upon expression of the antigen leads to an immune response against the antigen, Young et al. (US Patent Application Pub. 20040180002, September 15, 2004) teach that there have been many clinical trials of monoclonal antibodies for solid tumors. In the 1980s there were at least 4 clinical trials for human breast cancer which produced only 1 responder from at least 47 patients using antibodies against specific antigens or based on tissue selectivity. Young et al. teach that It was not until 1998 that there was a successful clinical trial using a humanized anti-her 2 antibody in combination with cisplatin (para 0010 of the published application). The same was true in clinical trials investigating colorectal cancer with antibodies against glycoprotein and glycolipid targets, wherein the specification specifically teaches "to date there has not been an antibody that has been effective for colorectal cancer. Likewise there have been equally poor results for lung, brain, ovarian, pancreatic, prostate and stomach cancers" (para 0011 of the published application). Thus, it is clear that the art recognizes that it could not be predicted, nor would it be expected in the absence of objective evidence demonstrating treatment of multidrug resistance in an appropriate model system in the specification or art of record, that it would be more likely than not that the

claimed SEQ ID NO: 3,or a complementary strand thereof, a recombinant vector containing SEQ ID NO: 3, a transformant that was transformed with the recombinant vector containing SEQ ID NO: 3, or a nucleic acid primers set forth in SEQ ID NO: 19 and 20 in the sequence listing which hybridize under stringent conditions with SEQ ID NO: 3 could be effectively used for the immunotherapeutic treatment of multidrug resistance without undue experimentation.

2) As drawn to anticancer gene therapy using administration of recombinant nucleic acids involving *in vivo* or *ex vivo* methods has not seen any success despite a great deal of work and resources. Several reviews in the art show that difficulties with vector selection, mode of delivery and persistence of predictable and effective levels of expression of the protein, created technical barriers to the practice of gene therapy methods. Verma et al. states that, "[t]he Achilles heel of gene therapy is gene delivery..." and that, "most of the approaches suffer from poor efficiency of delivery and transient expression of the gene" (Verma et al. (1997) Nature Volume 389, page 239, column 3, paragraph 2). Marshall concurs, stating that," difficulties in getting genes transferred efficiently to target cells- and getting them expressed-remain a nagging problem for the entire field", and that "many problems must be solved before genetherapy will be useful for more than the rare application" (Marshall (1995) Science, Volume 269, page 1054, column 3, paragraph 2, and page 1055, column 1).

Numerous factors complicate the gene therapy art, which have not been shown to be overcome by routine experimentation. Eck et al. (Goodman & Gilman's The Pharmacological Basis of Therapeutics (1996), 9th Edition, Chapter 5, McGraw-W, NY) explains, "the delivery of exogenous DNA and its processing by target cells requites the introduction of new pharmakinetic paradigms beyond those that describe the conventional medicines in use today". Eck et al. teaches

that with *in vivo* gene transfer, one must account for the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the in *vivo* consequences of altered gene expression and protein function, the fraction taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell or its secretory fat, once produced. These factors differ dramatically based on the vector used, the protein being produced and the disease being treated (see Eck et al. bridging pages 81-82).

Also among the many factors that the art teaches affect efficient gene delivery and sustained gene expressions are, immune responses and the identity of the promoter used to drive gene expression. Verma et al. teaches, in reference to *ex vivo* methods, that weak promoters produce only low levels of therapeutically effective protein, and that only by using appropriate enhancer-promoter combinations can sustained levels of therapeutically effective protein be achieved (Verma et al., *supra*, page 240, column 2). Verma et al. further warns that, ". . .the search for such combinations is a case of trial error for a given cell type" (Verma et al., *supra* , page 240, bridging sentence of columns 2-3). The state of the art is such that no correlation exists between successful expression of a gene and a therapeutic result (Ross et al. Human Gene Therapy,l996, Volume 7, pages 1781-1790, see page1789, column 1, first paragraph). Thus, the art at the at the time of filing clearly establishes that the expectation for achieving a desired therapeutic effect in vivo by expressing a therapeutic gene using any of the expression constructs known in the art was extremely low.

More recently, Rubanyi (Mol. Aspects Med. (2001) 22:113-142) teaches that the problems described above remain unresolved. Rubanyi states, "[although theoretical advantages of human gene therapy] are undisputable, so far [human gene therapy] has not delivered the promised results: convincing clinical efficacy could not be demonstrated yet in most of the trials conducted so far." (page 113, paragraph 1). Among the technical hurdles that Rubanyi teaches remain to be overcome are problems with gene delivery vectors and improvement in gene expression control systems (see section 3. "Technical hurdles to be overcome in the future", beginning on page 116 and continued through page 125). Furthermore, Juengst (British Medical Journal (2003) Volume 326, pages 1410-1411) teaches the unpredictable nature of gene therapy and that a few of the apparent successes actually developed T cell-acute lymphoblastic leukemia due to insertional mutagenesis at or near the LMO-2 gene causing altered gene expression. The art has demonstrated that a large amount of experimentation has already been performed without demonstrating successful gene therapy methods for treatment of disease. More recently, the unpredictability of delivery was further clarified by the tragic setback, in 2002, in the most celebrated clinical trial drawn to the treatment of SCID in children wherein gene therapy led to cancer because of insertional mutagenesis (see Cheek [Nature, 2002, 420:116-118]) wherein the NIH urged all investigators conducting retroviral-mediated gene transfer in hematopoietic cells to discontinue enrollment and administration of the experimental agent until new data are available (see Attached Letter of January 14, 2003, Exhibit 4).

Thus, in order to practice the claimed invention, the skilled artisan would not have found sufficient guidance in the specification to achieve effective levels of the expressed nucleic acid, to select a proper dose or administration route or to determine other factors for a successful treatment.

The prior art did not compensate for the lack of guidance in the specification since the teachings do not recognize any clearly successful gene therapy methods. The skilled artisan would have had to engage in a large amount of experimentation to practice the claimed invention. In view of the lack of guidance and the large amount of experimentation in an unpredictable art, it would require undue experimentation to practice the claimed invention.

Given the unpredictability in the arts of cancer therapeutics and gene therapy one of skill in the art would not believe more likely than not that the claimed pharmaceutical composition(s) would function as claimed for treating multidrug resistance without undue experimentation.

Applicant is reminded that MPEP 2164.03 teaches "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 428 F.2d 833, 166 USPQ 18, 24 (CCPA 1970) the amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly state in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order for it to be enabling. Given only lack of guidance in the specification, no one skilled in the art would accept the assertion that the claimed invention would function as contemplated or as claimed based only on the information in the specification and that known in the art at the time the invention was made.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention will function as contemplated or claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

12. Claims 4-8 and 17 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for SEQ ID NO: 3 coding for the polypeptide or protein according to claim 1, does not reasonably provide enablement for a nucleic hybridizing under stringent conditions with SEQ ID NO: 3 coding for the polypeptide or protein according to claim 1, a complementary strand to SEQ ID NO: 3 coding for the polypeptide or protein according to claim 1, or a nucleic acid represented by a base sequence comprising at least 15 consecutive bases of the base sequence of a nucleic acid set forth in SEQ ID NO: 3, wherein a polypeptide expressed by transcription for the nucleic acid is the polypeptide according to claim 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the

state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are broadly drawn to a nucleic hybridizing under stringent conditions with SEQ ID NO: 3 coding for the polypeptide or protein according to claim 1, a complementary strand to SEQ ID NO: 3 coding for the polypeptide or protein according to claim 1, or a nucleic acid represented by a base sequence comprising at least 15 consecutive bases of the base sequence of a nucleic acid set forth in SEQ ID NO: 3, wherein a polypeptide expressed by transcription for the nucleic acid is the polypeptide according to claim 1.

This means that any nucleic hybridizing under stringent conditions with SEQ ID NO: 3, complementary strand to SEQ ID NO: 3, or a nucleic acid represented by a base sequence comprising at least 15 consecutive bases of the base sequence of a nucleic acid set forth in SEQ ID NO: 3 can code for a protein or polypeptide according to claim 1, which is a protein that is present in the nucleus of animal cell and which has transcription factor function and/or a function that can induce expression of the RB1 gene.

The specification teaches as set forth above.

The specification teaches that the term "nucleic acid and a complementary strand thereof" of the present invention refers to a nucleic acid set forth in SEQ ID No: 3 or 4 in the sequence listing that codes for an amino acid sequence set forth in SEQ ID No: 1 or 2 in the sequence listing and the complementary strand for the nucleic acid, a nucleic acid hybridizing under stringent conditions with these nucleic acids, and a nucleic acid having a sequence of at least 15 consecutive base sequence derived from these nucleic acids in which a peptide encoded thereby is capable of binding with an antibody against the novel protein RB1CC1. The specification teaches that the term

"hybridizing under stringent conditions" refers to, for example, conditions under which a positive hybridization signal is still observed even after heating at 42°C in a solution of 6X.SSC, 0.5% SDS and 50% formamide, and washing at 68 °C in a solution of 0.1.XSSC and 0.5% SDS, see [Nucleic acid] p. 21-22.

It is noted that the definitions of a complementary strand and a nucleic acid hybridizing under stringent conditions are none limiting and do not limit the claims to nucleic acids that are completely complementary or hybridize to the full length of SEQ ID NO: 3.

One cannot extrapolate the teachings of the specification to the scope of the claims because the claims are drawn to nucleic acids that are not the full length SEQ ID NO: 3 and one of skill in the art would not predict that polypeptide fragments encoded by the nucleic acid fragments of SEQ ID NO: 3 would predictably be present in the nucleus of an animal cell and have a transcription factor function and/or induce expression of the RB1 gene because of the unpredictability of protein biochemistry is well known in the art.

In particular, Bowie et al (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col. 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are

critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col. 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. Further, Scott et al (Nature Genetics, 1999, 21:440-443) teach that the gene causing Pendred syndrome encodes a putative transmembrane protein designated pendrin. Based on sequence similarity data, the authors postulated that the putative protein was deemed to be a member of sulfate transport protein family since the putative protein had a 29% identity to rat sulfate-anion transporter, 32% similarity to human diastrophic dysplasia sulfate transporter and 45% similarity to the human sulfate transporter. However, upon analyzing the expression and kinetics of the protein, the data revealed no evidence of sulfate transport activity wherein results revealed that pendrin functioned as a transporter of chloride and iodide. Scott et al suggest that these results underscore the importance of confirming the function of newly identified gene products even when database searched reveal significant homology to proteins of known function (page 411, 1st column, 4th paragraph). In addition, Bork (Genome Research, 2000,10:398-400) clearly teaches the pitfalls associated with comparative sequence analysis for predicting

protein function because of the known error margins for high-throughput computational methods. Bork specifically teaches that computational sequence analysis is far from perfect, despite the fact that sequencing itself is highly automated and accurate (p. 398, col. 1). One of the reasons for the inaccuracy is that the quality of data in public sequence databases is still insufficient. This is particularly true for data on protein function. Protein function is context dependent, and both molecular and cellular aspects have to be considered (p. 398, col. 2). Conclusions from the comparison analysis are often stretched with regard to protein products (p. 398, col. 3). Furthermore, recent studies show that alternative splicing might affect more than 30% of human genes and the number of known post-translational modifications of gene products is increasing constantly so that complexity at protein level is enormous. Each of these modifications may change the function of respective gene products drastically (p. 399, col. 1). Further, although gene annotation via sequence database searches is already a routine job, even here the error rate is considerable (p. 399, col. 2). Most features predicted with an accuracy of greater than 70% are of structural nature and at best only indirectly imply a certain functionality (see legend for table 1, page 399). As more sequences are added and as errors accumulate and propagate it becomes more difficult to infer correct function from the many possibilities revealed by database search (p. 399para bridging cols 2 and 3). The reference finally cautions that although the current methods seem to capture important features and explain general trends, 30% of those features are missing or predicted wrongly. This has to be kept in mind when processing the results further (p. 400, para bridging cols 1 and 2). The teachings of Bork are clearly illustrated by Pero et al. (US PG Pub 20030105000) who specifically teach in Example 4 that the SH2 domain of Grb14 is 81% similar to the SH2 domain of Grb7 on the amino acid level, but although Grb7 binds to ErbB2, Grb14 does

not bind to ErbB2. Further, although the SH2 domain of Grb2 is only 50 % similarity to Grb 7 on the amino acid level, both Grb2 and Grb7 bind to the same site on ErbB2. Thus, sequence identity or similarity alone cannot be used to predict the function of a protein.

Clearly, given not only the teachings of Bowie et al, Lazar et al, Burgess et al, Scott et al. and Pero et al., but also the limitations and pitfalls of using computational sequence analysis and the unknown effects of alternative splicing, post translational modification and cellular context on protein function as taught by Bork, the effects on the function of a protein encoded by SEQ ID NO: 3 by a nucleic hybridizing under stringent conditions with SEQ ID NO: 3, a complementary strand to SEQ ID NO: 3, or a nucleic acid represented by a base sequence comprising at least 15 consecutive bases of the base sequence of a nucleic acid set forth in SEQ ID NO: 3 can code for a protein or polypeptide according to claim 1 cannot be predicted. The specification does not teach the critical residues that are required for the function of the protein encoded by SEQ ID NO: 3, RB1CC1. Thus given what is known in the art about the unpredictability of the effect of changes of protein structure on protein function one cannot predict the effect of the claimed unknown and undefined changes in protein structure would have on the ability of the contemplated nucleic acid fragments to code for a protein the functions as contemplated in claim 1.

Applicant is reminded that MPEP 2164.03 teaches "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 428 F.2d 833, 166 USPQ 18, 24 (CCPA 1970) the amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more

predictable the art is, the less information needs to be explicitly state in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order for it to be enabling. Given only lack of guidance in the specification, no one skilled in the art would accept the assertion that the claimed invention would function as contemplated or as claimed based only on the information in the specification and that known in the art at the time the invention was made.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention will function as contemplated with a reasonable expectation of success. For the above reasons, it appear that undue experimentation would be required to practice the claimed invention.

13. Claims 4-8 and 17 are rejected under 35 USC 112, first paragraph, as lacking an adequate written description in the specification.

Claims 4-8 and 17 are broadly drawn to complementary strands of SEQ ID NO: 3, nucleic acids hybridizing under stringent conditions to SEQ ID NO: 3, and a nucleic acid comprising at least 15 consecutive bases of the base sequence of a nucleic acid set forth in SEQ ID NO: 3.

Although claim 1 requires the protein to have a transcription factor function and/or induce expression of the RB1 gene the critical residues for these functions have not been identified.

The state of the art is such that it is well know in the art that complementary strands of nucleic acids include nucleic strands that are less than full length molecules and range from those that lack significant complementarity to those that are completely complementary to the claimed

polynucleotide in view of the teaching of US Patent No. 5,912,143 that teaches that the term complementary refers to the natural binding of polynucleotides under permissive salt and temperature conditions and specifically teaches that complementarity between two single-stranded molecules may be "partial" or it may be "complete" (col. 5, lines 19-32). It is noted that claim 5 is drawn to nucleic acids hybridizing under stringent conditions to SEQ ID NO: 3. However, the specification does not define hybridizing under stringent conditions in a limiting manner and the claim does not define hybridization conditions, therefore, it is assumed for examination purposes that hybridizing under stringent conditions include the entire range of stringent conditions from very low, or permissive to very high stringency and thus the claimed hybridized polynucleotides read on polynucleotides that range from those that lack significant complementarity to those that are completely complementary.

Given the above, it is clear that an adequate written description is essential for one of skill in the art to make and use the claimed invention.

As it is drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here.

Thus, the instant specification may provide an adequate written description of complementary strands of SEQ ID NO: 3, nucleic acids hybridizing under stringent conditions to SEQ ID NO: 3, and a nucleic acid comprising at least 15 consecutive bases of the base sequence of a nucleic acid set forth in SEQ ID NO: 3, per Lilly by structurally describing a representative number of complementary strands of SEQ ID NO: 3, nucleic acids hybridizing under stringent conditions to SEQ ID NO: 3, and a nucleic acid comprising at least 15 consecutive bases of the base sequence of a nucleic acid set forth in SEQ ID NO: 3, or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not describe complementary strands of SEQ ID NO: 3, nucleic acids hybridizing under stringent conditions to SEQ ID NO: 3, and a nucleic acid comprising at least 15 consecutive bases of the base sequence of a nucleic acid set forth in SEQ ID NO: 3, in a manner that satisfies either the Lilly or Enzo standards. The specification does not provide the complete structure of any complementary strands of SEQ ID NO: 3, nucleic acids hybridizing under stringent conditions to SEQ ID NO: 3, and a nucleic acid comprising at least 15 consecutive bases of the base sequence of a nucleic acid set forth in SEQ ID NO: 3, nor does the specification provide any partial structure of such polypeptides, nor any physical or chemical

characteristics of complementary strands of SEQ ID NO: 3, nucleic acids hybridizing under stringent conditions to SEQ ID NO: 3, and a nucleic acid comprising at least 15 consecutive bases of the base sequence of a nucleic acid set forth in SEQ ID NO: 3, nor any functional characteristics coupled with a known or disclosed correlation between structure and function. Although the specification discloses SEQ ID NO: 3, this does not provide a description of complementary strands of SEQ ID NO: 3, nucleic acids hybridizing under stringent conditions to SEQ ID NO: 3, and a nucleic acid comprising at least 15 consecutive bases of the base sequence of a nucleic acid set forth in SEQ ID NO: 3 that would satisfy the standard set out in Enzo.

The specification also fails to describe complementary strands of SEQ ID NO: 3, nucleic acids hybridizing under stringent conditions to SEQ ID NO: 3, and a nucleic acid comprising at least 15 consecutive bases of the base sequence of a nucleic acid set forth in SEQ ID NO: 3 by the test set out in Lilly. The specification describes only SEQ ID NO: 3. Therefore, it necessarily fails to describe a "representative number" of such species. In addition, the specification also does not describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus."

Thus, the specification does not provide an adequate written description of complementary strands of SEQ ID NO: 3, nucleic acids hybridizing under stringent conditions to SEQ ID NO: 3, and a nucleic acid comprising at least 15 consecutive bases of the base sequence of a nucleic acid set forth in SEQ ID NO: 3 that is required to practice the claimed invention or reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the broadly claimed invention.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 4-6 and 17 rejected under 35 U.S.C. 102(b) as being anticipated by AB059622 (October 11, 2001) as evidenced by Chano et al. (Oncogene, February 14, 2002, 21:1295-1298, IDS, see exhibit 3 for date) and Exhibits 1 and 2.

It is noted that the preamble recitation of a pharmaceutical composition for use in treatment of multidrug resistance that is resistance to treatment with anticancer agents is merely suggestive of an intended use and is not given weight for purposes of comparing the claims with the prior art. The claims read on the product per se, i. e. SEQ ID NO: 3, a recombinant vector containing SEQ ID NO: 3, or a transformant transformed with a recombinant vector containing SEQ ID NO: 3.

The claims are drawn to:

3. A nucleic acid coding for the polypeptide or protein according to claim 1, SEQ ID NO: 3, or a complementary strand thereof.

5. A nucleic acid hybridizing under stringent conditions with the nucleic acid according to claim 3 or the complementary strand thereof.

6. A nucleic acid represented by a base sequence comprising at least 15 consecutive bases of the base sequence of a nucleic acid set forth in SEQ ID NO: 3 in the sequence listing or a complementary strand thereof, wherein a polypeptide expressed by transcription of the nucleic acid is the polypeptide according to claim 1.

17. A pharmaceutical composition for use in treatment of multidrug resistance that is resistance to treatment with anticancer agents, wherein the pharmaceutical composition comprises a nucleic acid coding for the polypeptide or protein or a complementary strand thereof according to claim 1

(SEQ ID NO: 3), a recombinant vector containing the nucleic acid, a transformant that was transformed with the recombinant vector, listing which hybridize under stringent conditions with the nucleic acid.

AB059622 teaches a sequence that is identical to SEQ ID NO: 3, see Exhibit 1. Given the identity of the prior art molecule to the instantly claimed molecule, it inherently would encode a polypeptide with the properties set forth for the protein of claim 1.

Exhibit 2 teaches that AB059622 was publicly available October 11, 2001.

Further, Chano et al. teach the protein encoded by AB059622, RB1CC1, can induce the expression of the RB1 gene, see Abstract, Fig. 2 and Fig.4.

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

15. Claims 7-10 are rejected under 35 U.S.C. 102(a) as being anticipated by Chano et al. (Oncogene, February 14, 2002, 21:1295-1298, IDS, see Exhibit 3 for date) as evidenced by Exhibit 2.

The claims are drawn to:

7. A recombinant vector containing the nucleic acid according to claim 4.

8. A transformant that was transformed with the recombinant vector according to claim 7.

9. A method for producing the polypeptide or protein according to claim 1, comprising a step of culturing the transformant with the recombinant vector containing nucleic acid coding for the polypeptide or protein.

10. Nucleic acid primers set forth in SEQ ID NO: 19 and 20 in the sequence listing, which hybridize under stringent conditions with the nucleic acid according to claim 4 or the complementary strand thereof.

17. A pharmaceutical composition for use in treatment of multidrug resistance that is resistance to treatment with anticancer agents, wherein the pharmaceutical composition comprises nucleic acid primers set forth in SEQ ID NO: 19 and 20 in the sequence listing which hybridize under stringent conditions with SEQ ID NO: 3.

It is noted that the preamble recitation of a pharmaceutical composition for use in treatment of multidrug resistance that is resistance to treatment with anticancer agents is merely suggestive of an intended use and is not given weight for purposes of comparing the claims with the prior art. The claims read on the product per se, i.e. nucleic acid primers set forth in SEQ ID NO: 19 and 20 in the sequence listing which hybridize under stringent conditions with SEQ ID NO: 3.

It is also noted that although the claims are being examined as drawn to SEQ ID NO: 3 and variants thereof, the claims does not limit the nucleic acid in the recombinant vector to being the full length SEQ ID NO: 3.

AB059622 teaches a sequence that is identical to SEQ ID NO: 3, see Exhibit 2

Chano et al. teach a transforming a recombinant vector containing the cDNA encoding the RB1CC1 protein into K562 and Jurkat cell lines, see Fig. 4. Chano et al. teach the protein encoded by AB059622, RB1CC1, can induce the expression of the RB1 gene, see Abstract, Fig.2 and Fig.4. Chano et al. teach that SEQ ID NO: 19 and SEQ ID NO: 20 were used in RT-PCR amplification of RB1CC1, see Fig. 3, Primers CC1S and CC1AS.

The method of the prior art comprises the same method steps as claimed in claimed 9, that is, comprising a step of culturing the transformant with the recombinant vector containing nucleic acid coding for the polypeptide or protein according to claim 1, thus the claimed method is anticipated because the method will inherently be a method for producing the polypeptide or protein

according to claim 1, See Ex parte Novitski 26 USPQ 1389 (BPAI 1993). Although the reference does not specifically state that the method is a method for producing the polypeptide or protein according to claim 1, the claimed method appears to be the same as the prior art method, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the method of the prior art does not possess the same material, structural and functional characteristics of the claimed method. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed method is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

16. Claims 10 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over AB059622 (October 11, 2001), in view of Mensink et al (British J. Haematol. (August 1998) 102:768-774) and further in view of Buck et al (Biotechniques (1999) 27(3):528-536).

The claims are drawn to:

10. Nucleic acid primers set forth in SEQ ID NO: 19 and 20 in the sequence listing, which hybridize under stringent conditions with the nucleic acid according to claim 4 or the complementary strand thereof.

17. A pharmaceutical composition for use in treatment of multidrug resistance that is resistance to treatment with anticancer agents, wherein the pharmaceutical composition comprises nucleic acid primers set forth in SEQ ID NO: 19 and 20 in the sequence listing which hybridize under stringent conditions with SEQ ID NO: 3.

It is noted that the preamble recitation of a pharmaceutical composition for use in treatment of multidrug resistance that is resistance to treatment with anticancer agents is merely suggestive of

an intended use and is not given weight for purposes of comparing the claims with the prior art. The claims read on the product per se, i.e. nucleic acid primers set forth in SEQ ID NO: 19 and 20 in the sequence listing which hybridize under stringent conditions with SEQ ID NO: 3.

AB059622 (October 11, 2001) teach SEQ ID NO: 3 as set forth above.

AB059622 does not teach the particular primers of SEQ ID NO: 19 and 20.

Mensink teaches primer selection, "Using the Primer Express software program (Perkin-Elmer, Foster City, Calif. Demo version 1.0 ppd) we designed PCR primers for the amplification of cDNA derived from the BCR-ABL transcript and PBGD transcript (page 769, column 2)".

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the method of Mensink to produce primers selected from the sequences of AB059622 since Mensink expressly teaches primer selection using commercially available software for BCR-ABL detection from the BCR-ABL published sequences and since AB059622 provide such published sequences for the software program to analyze.

In the recent court decision KSR International Co. v. Teleflex Inc., the U.S. Supreme court determined that "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under §103." KSR International Co. v. Teleflex Inc., 82 USPQ2d 1385 (U.S. 2007)

Since the claimed primers simply represent structural homologs of SEQ ID NO: 3 that are derived from sequences suggested by the prior art as useful for primers for SEQ ID NO: 3 and

would predictably be within the technical grasp of one of ordinary skill in the art to make, the claimed primers are *prima facie* obvious over the cited references in the absence of secondary considerations.

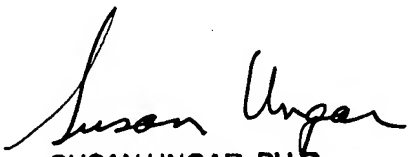
Buck expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

16. No claims allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter J. Reddig whose telephone number is (571) 272-9031. The examiner can normally be reached on M-F 8:30 a.m.-5:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on (571) 272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



SUSAN UNGAR, PH.D
PRIMARY EXAMINER

Peter J. Reddig
Examiner
Art Unit 1642

PJR

Exhibit 1

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AB059622
LOCUS       AB059622                6636 bp    mRNA    linear   PRI 10-JUL-2002
DEFINITION  Homo sapiens RBICC mRNA for Rb1-inducible coiled coil protein,
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ACCESSION   AB059622
VERSION     AB059622.1  GI:16040976
KEYWORDS    .
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
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            Catarrhini; Hominidae; Homo.
REFERENCE   1
  AUTHORS   Chano,T., Ikegawa,S., Kontani,K., Okabe,H., Baldini,N. and Saeki,Y.
  TITLE     Identification of RB1CC1, a novel human gene that can induce RB1 in
            various human cells
  JOURNAL   Oncogene 21 (8), 1295-1298 (2002)
   PUBMED   11850849
REFERENCE   2
  AUTHORS   Chano,T., Ikegawa,S., Saito-Ohara,F., Inazawa,J., Mabuchi,A.,
            Saeki,Y. and Okabe,H.
  TITLE     Isolation, characterization and mapping of the mouse and human
            RB1CC1 genes
  JOURNAL   Gene 291 (1-2), 29-34 (2002)
   PUBMED   12095676
REFERENCE   3  (bases 1 to 6636)
  AUTHORS   Chano,T.
  TITLE     Direct Submission
  JOURNAL   Submitted (10-APR-2001) Tokuhiro Chano, Shiga University of Medical
            Science, Department of Clinical Laboratory Medicine; Seta,
            Tsukinowa, Otsu, Shiga 520-2192, Japan
            (E-mail:chano@belle.shiga-med.ac.jp, Tel:81-77-548-2600(ex.2600),
            Fax:81-77-548-2407)
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ORIGIN

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Qy        301 TGGTGCCGGGGGTCGCTGGCTCTGCTGCTGCCGCCGGCGAAGGAGGAGGCGTTGCCGGTT 360
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
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Db        301 TGGTGCCGGGGGTCGCTGGCTCTGCTGCTGCCGCCGGCGAAGGAGGAGGCGTTGCCGGTT 360

Qy        361 TTCTGAGTTTAACCAGTAATGCCATTCAGTTGCCAATCTCAAGCAAAGCAAACATAAGCC 420
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        361 TTCTGAGTTTAACCAGTAATGCCATTCAGTTGCCAATCTCAAGCAAAGCAAACATAAGCC 420

Qy        421 AGTTTTAATCTACTTTTTAAGAAAAGTGGTAGTCCTTTTCACAGTGCCTGACGTAACTGT 480
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        421 AGTTTTAATCTACTTTTTAAGAAAAGTGGTAGTCCTTTTCACAGTGCCTGACGTAACTGT 480

Qy        481 ATCAGAGGGTGAGGTATAAGCTCACAGAATTCAGATAAATCATCATGAAGTTATATGTAT 540
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        481 ATCAGAGGGTGAGGTATAAGCTCACAGAATTCAGATAAATCATCATGAAGTTATATGTAT 540

Qy        541 TTCTGGTTAACACTGGAACTACTCTAACATTTGACACTGAACTTACAGTGCAAACTGTGG 600
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        541 TTCTGGTTAACACTGGAACTACTCTAACATTTGACACTGAACTTACAGTGCAAACTGTGG 600

Qy        601 CAGACCTTAAGCATGCCATTCAAAGCAAATACAAGATTGCTATTCAACACCAGGTGCTGG 660
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        601 CAGACCTTAAGCATGCCATTCAAAGCAAATACAAGATTGCTATTCAACACCAGGTGCTGG 660

Qy        661 TGGTCAATGGAGGAGAATGCATGGCTGCAGATCGAAGAGTGTGTACCTACAGTGCTGGGA 720
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        661 TGGTCAATGGAGGAGAATGCATGGCTGCAGATCGAAGAGTGTGTACCTACAGTGCTGGGA 720

Qy        721 CGGATACAAATCCAATTTTTCTTTTTAACAAAGAAATGATCTTATGCGATCGTCCACCTG 780
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        721 CGGATACAAATCCAATTTTTCTTTTTAACAAAGAAATGATCTTATGCGATCGTCCACCTG 780

Qy        781 CTATTCCTAAAACTACCTTTTCGACAGAAAATGACATGGAAATAAAAGTTGAAGAATCTC 840
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        781 CTATTCCTAAAACTACCTTTTCGACAGAAAATGACATGGAAATAAAAGTTGAAGAATCTC 840

Qy        841 TTATGATGCCTGCAGTTTTTCATACTGTTGCTTCAAGGACACAGCTTGCATTGGAAATGT 900
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        841 TTATGATGCCTGCAGTTTTTCATACTGTTGCTTCAAGGACACAGCTTGCATTGGAAATGT 900

Qy        901 ATGAAGTTGCCAAGAAACTTTGTTCTTTTTGTGAAGGTCTTGTACATGATGAACATCTTC 960
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        901 ATGAAGTTGCCAAGAAACTTTGTTCTTTTTGTGAAGGTCTTGTACATGATGAACATCTTC 960

Qy        961 AACACCAAGGCTGGGCTGCAATCATGGCCAACCTGGAGGACTGTTCAAATTCATACCAAA 1020
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        961 AACACCAAGGCTGGGCTGCAATCATGGCCAACCTGGAGGACTGTTCAAATTCATACCAAA 1020

Qy       1021 AGCTACTTTTCAAGTTTGAAAGTATTTATTCAAATTATCTGCAGTCCATAGAAGACATCA 1080
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1021 AGCTACTTTTCAAGTTTGAAAGTATTTATTCAAATTATCTGCAGTCCATAGAAGACATCA 1080

Qy       1081 AGTTAAAACTTACTCATTTAGGAACTGCAGTTTCAGTAATGGCCAAGATTCCACTGTTGG 1140
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1081 AGTTAAAACTTACTCATTTAGGAACTGCAGTTTCAGTAATGGCCAAGATTCCACTGTTGG 1140
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Qy       1141 AGTGCCTAACCAGACATAGTTACAGAGAATGTTTGGGAAGACTGGATTCTTTACCTGAAC 1200
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1141 AGTGCCTAACCAGACATAGTTACAGAGAATGTTTGGGAAGACTGGATTCTTTACCTGAAC 1200

Qy       1201 ATGAAGACTCAGAAAAAGCTGAGACGAAAAGATCCACTGAACTGGTGCTCTCTCCTGATA 1260
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1201 ATGAAGACTCAGAAAAAGCTGAGACGAAAAGATCCACTGAACTGGTGCTCTCTCCTGATA 1260

Qy       1261 TGCCTAGAACAACTAACGAATCTTTGTTAACCTCATTTCCCAAGTCAGTGGAACATGTGT 1320
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1261 TGCCTAGAACAACTAACGAATCTTTGTTAACCTCATTTCCCAAGTCAGTGGAACATGTGT 1320

Qy       1321 CCCCAGATACCGCAGATGCTGAAAGTGGCAAAGAAATTAGGGAATCTTGTCAAAGTACTG 1380
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1321 CCCCAGATACCGCAGATGCTGAAAGTGGCAAAGAAATTAGGGAATCTTGTCAAAGTACTG 1380

Qy       1381 TTCATCAGCAAGATGAAACTACGATTGACACTAAAGATGGTGATCTGCCCTTTTTTAATG 1440
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1381 TTCATCAGCAAGATGAAACTACGATTGACACTAAAGATGGTGATCTGCCCTTTTTTAATG 1440

Qy       1441 TCTCTTTGTTAGACTGGATAAATGTTCAAGATAGACCTAATGATGTGGAATCTTTGGTCA 1500
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1441 TCTCTTTGTTAGACTGGATAAATGTTCAAGATAGACCTAATGATGTGGAATCTTTGGTCA 1500

Qy       1501 GGAAGTGCTTTGATTCTATGAGCAGGCTTGATCCAAGGATTATTCGACCATTTATAGCAG 1560
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1501 GGAAGTGCTTTGATTCTATGAGCAGGCTTGATCCAAGGATTATTCGACCATTTATAGCAG 1560

Qy       1561 AATGCCGTCAAACTATTGCCAAACTTGATAATCAGAATATGAAAGCCATTAAAGGACTTG 1620
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1561 AATGCCGTCAAACTATTGCCAAACTTGATAATCAGAATATGAAAGCCATTAAAGGACTTG 1620

Qy       1621 AAGATCGGCTCTACGCCCTGGACCAGATGATTGCTAGCTGTGGCCGACTGGTGAATGAAC 1680
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1621 AAGATCGGCTCTACGCCCTGGACCAGATGATTGCTAGCTGTGGCCGACTGGTGAATGAAC 1680

Qy       1681 AGAAAGAGCTTGCTCAGGGATTTTTAGCTAATCAGAAGAGAGCTGAAAACTTAAAGGATG 1740
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1681 AGAAAGAGCTTGCTCAGGGATTTTTAGCTAATCAGAAGAGAGCTGAAAACTTAAAGGATG 1740

Qy       1741 CATCTGTATTACCTGATTTATGCCTGAGTCACGCAAATCAGTTGATGATTATGTTGCAAA 1800
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1741 CATCTGTATTACCTGATTTATGCCTGAGTCACGCAAATCAGTTGATGATTATGTTGCAAA 1800

Qy       1801 ATCATAGAAAACTGTTAGATATTAAGCAGAAGTGTACCACTGCCAAACAAGAACTAGCAA 1860
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1801 ATCATAGAAAACTGTTAGATATTAAGCAGAAGTGTACCACTGCCAAACAAGAACTAGCAA 1860

Qy       1861 ATAACCTACATGTCAGACTGAAGTGGTGTTGCTTTGTAATGCTTCATGCTGATCAAGATG 1920
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1861 ATAACCTACATGTCAGACTGAAGTGGTGTTGCTTTGTAATGCTTCATGCTGATCAAGATG 1920

Qy       1921 GAGAGAAGTTACAAGCTTTGCTCCGCCTCGTAATAGAGCTGTTAGAAAGAGTCAAAATTG 1980
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
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Db       1921 GAGAGAAGTTACAAGCTTTGCTCCGCCTCGTAATAGAGCTGTTAGAAAGAGTCAAAATTG 1980

Qy       1981 TTGAAGCTCTTAGTACAGTTCCTCAGATGTACTGCTTAGCTGTTGTTGAGGTTGTAAGAA 2040
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1981 TTGAAGCTCTTAGTACAGTTCCTCAGATGTACTGCTTAGCTGTTGTTGAGGTTGTAAGAA 2040

Qy       2041 GAAAAATGTTCATAAAACACTACAGGGAGTGGGCTGGTGCTTTAGTCAAAGATGGAAAGA 2100
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2041 GAAAAATGTTCATAAAACACTACAGGGAGTGGGCTGGTGCTTTAGTCAAAGATGGAAAGA 2100

Qy       2101 GATTATATGAAGCAGAAAAATCAAAAAGGGAATCCTTTGGGAAATTATTTAGGAAGTCTT 2160
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2101 GATTATATGAAGCAGAAAAATCAAAAAGGGAATCCTTTGGGAAATTATTTAGGAAGTCTT 2160

Qy       2161 TTTTAAGAAATCGTCTGTTTAGGGGACTGGACTCCTGGCCCCCTTCCTTTTGTACTCAAA 2220
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2161 TTTTAAGAAATCGTCTGTTTAGGGGACTGGACTCCTGGCCCCCTTCCTTTTGTACTCAAA 2220

Qy       2221 AGCCTCGAAAGTTTGACTGTGAACTTCCAGATATTTCATTAAAAGATTTACAGTTTCTGC 2280
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2221 AGCCTCGAAAGTTTGACTGTGAACTTCCAGATATTTCATTAAAAGATTTACAGTTTCTGC 2280

Qy       2281 AATCATTTTGTCCTTCGGAAGTTCAGCCATTCCTCAGGGTTCCCTTACTTTGTGACTTTG 2340
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2281 AATCATTTTGTCCTTCGGAAGTTCAGCCATTCCTCAGGGTTCCCTTACTTTGTGACTTTG 2340

Qy       2341 AACCTCTACACCAGCATGTACTTGCTCTACATAATTTGGTAAAAGCAGCACAAAGTTTGG 2400
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2341 AACCTCTACACCAGCATGTACTTGCTCTACATAATTTGGTAAAAGCAGCACAAAGTTTGG 2400

Qy       2401 ATGAAATGTCACAGACCATTACAGATCTACTGAGTGAACAAAAGGCATCTGTGAGCCAGA 2460
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2401 ATGAAATGTCACAGACCATTACAGATCTACTGAGTGAACAAAAGGCATCTGTGAGCCAGA 2460

Qy       2461 CATCCCCACAGTCTGCTTCTTCACCAAGGATGGAAAGTACAGCAGGAATTACAACTACTA 2520
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2461 CATCCCCACAGTCTGCTTCTTCACCAAGGATGGAAAGTACAGCAGGAATTACAACTACTA 2520

Qy       2521 CCTCACCGAGAACTCCTCCACCACTGACTGTTCAGGATCCCTTATGTCCTGCAGTTTGTC 2580
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2521 CCTCACCGAGAACTCCTCCACCACTGACTGTTCAGGATCCCTTATGTCCTGCAGTTTGTC 2580

Qy       2581 CCTTAGAAGAATTATCTCCAGATAGTATTGATGCACATACGTTTGATTTTGAAACTATTC 2640
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2581 CCTTAGAAGAATTATCTCCAGATAGTATTGATGCACATACGTTTGATTTTGAAACTATTC 2640

Qy       2641 CCCATCCAAACATAGAACAGACTATTCACCAAGTTTCTTTAGACTTGGATTCATTAGCAG 2700
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2641 CCCATCCAAACATAGAACAGACTATTCACCAAGTTTCTTTAGACTTGGATTCATTAGCAG 2700

Qy       2701 AAAGTCCTGAATCAGATTTTATGTCTGCTGTGAATGAGTTTGTAATAGAAGAAAATTTGT 2760
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2701 AAAGTCCTGAATCAGATTTTATGTCTGCTGTGAATGAGTTTGTAATAGAAGAAAATTTGT 2760
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Qy       2761 CGTCTCCTAATCCTATAAGTGATCCACAAAGCCCAGAAATGATGGTGGAATCACTTTATT 2820
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2761 CGTCTCCTAATCCTATAAGTGATCCACAAAGCCCAGAAATGATGGTGGAATCACTTTATT 2820

Qy       2821 CATCAGTTATCAATGCGATAGACAGTAGACGAATGCAGGATACAAATGTATGTGGTAAGG 2880
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2821 CATCAGTTATCAATGCGATAGACAGTAGACGAATGCAGGATACAAATGTATGTGGTAAGG 2880

Qy       2881 AGGATTTTGGAGATCATACTTCTCTGAATGTCCAGTTGGAAAGATGTAGAGTTGTTGCCC 2940
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2881 AGGATTTTGGAGATCATACTTCTCTGAATGTCCAGTTGGAAAGATGTAGAGTTGTTGCCC 2940

Qy       2941 AAGACTCTCACTTCAGTATACAAACCATTAAGGAAGACCTTTGCCACTTTAGAACATTTG 3000
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2941 AAGACTCTCACTTCAGTATACAAACCATTAAGGAAGACCTTTGCCACTTTAGAACATTTG 3000

Qy       3001 TACAAAAAGAACAGTGTGACTTCTCAAATTCATTAAAATGTACAGCAGTAGAAATAAGAA 3060
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3001 TACAAAAAGAACAGTGTGACTTCTCAAATTCATTAAAATGTACAGCAGTAGAAATAAGAA 3060

Qy       3061 ACATTATTGAAAAAGTAAAATGTTCTCTGGAAATAACACTAAAAGAAAAACATCAAAAAG 3120
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3061 ACATTATTGAAAAAGTAAAATGTTCTCTGGAAATAACACTAAAAGAAAAACATCAAAAAG 3120

Qy       3121 AACTACTGTCTTTAAAAAATGAATATGAAGGTAAACTTGACGGACTAATAAAGGAAACTG 3180
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3121 AACTACTGTCTTTAAAAAATGAATATGAAGGTAAACTTGACGGACTAATAAAGGAAACTG 3180

Qy       3181 AAGAGAATGAAAACAAAATTAAAAAATTGAAGGGAGAGTTAGTATGCCTTGAGGAGGTTT 3240
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3181 AAGAGAATGAAAACAAAATTAAAAAATTGAAGGGAGAGTTAGTATGCCTTGAGGAGGTTT 3240

Qy       3241 TACAAAATAAAGATAATGAATTTGCTTTGGTTAAACATGAAAAAGAAGCTGTAATCTGCC 3300
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3241 TACAAAATAAAGATAATGAATTTGCTTTGGTTAAACATGAAAAAGAAGCTGTAATCTGCC 3300

Qy       3301 TGCAGAATGAAAAGGATCAGAAGTTGTTAGAGATGGAAAATATAATGCACTCTCAAAATT 3360
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3301 TGCAGAATGAAAAGGATCAGAAGTTGTTAGAGATGGAAAATATAATGCACTCTCAAAATT 3360

Qy       3361 GTGAAATTAAAGAACTGAAGCAGTCACGAGAAATAGTGTTAGAAGACTTAAAAAAGCTCC 3420
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3361 GTGAAATTAAAGAACTGAAGCAGTCACGAGAAATAGTGTTAGAAGACTTAAAAAAGCTCC 3420

Qy       3421 ATGTTGAAAATGATGAGAAGTTACAGTTATTGAGGGCAGAACTTCAGTCCTTGGAGCAAA 3480
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3421 ATGTTGAAAATGATGAGAAGTTACAGTTATTGAGGGCAGAACTTCAGTCCTTGGAGCAAA 3480

Qy       3481 GTCATCTAAAGGAATTAGAGGACACACTTCAGGTTAGGCACATACAAGAGTTTGAGAAGG 3540
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3481 GTCATCTAAAGGAATTAGAGGACACACTTCAGGTTAGGCACATACAAGAGTTTGAGAAGG 3540

Qy       3541 TTATGACAGACCACAGAGTTTCTTTGGAGGAATTAAAAAAGGAAAATCAACAAATAATTA 3600
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
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Db       3541 TTATGACAGACCACAGAGTTTCTTTGGAGGAATTAAAAAAGGAAAATCAACAAATAATTA 3600

Qy       3601 ATCAAATACAAGAATCTCATGCTGAAATTATCCAGGAAAAAGAAAAACAGTTACAGGAAT 3660
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3601 ATCAAATACAAGAATCTCATGCTGAAATTATCCAGGAAAAAGAAAAACAGTTACAGGAAT 3660

Qy       3661 TAAAACTCAAGGTTTCTGATTTGTCAGACACGAGATGCAAGTTAGAGGTTGAACTTGCGT 3720
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3661 TAAAACTCAAGGTTTCTGATTTGTCAGACACGAGATGCAAGTTAGAGGTTGAACTTGCGT 3720

Qy       3721 TGAAGGAAGCAGAAACTGATGAAATAAAAATTTTGCTGGAAGAAAGCAGAGCCCAGCAGA 3780
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3721 TGAAGGAAGCAGAAACTGATGAAATAAAAATTTTGCTGGAAGAAAGCAGAGCCCAGCAGA 3780

Qy       3781 AGGAGACCTTGAAATCTCTTCTTGAACAAGAGACAGAAAATTTGAGAACAGAAATTAGTA 3840
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3781 AGGAGACCTTGAAATCTCTTCTTGAACAAGAGACAGAAAATTTGAGAACAGAAATTAGTA 3840

Qy       3841 AACTCAACCAAAAGATTCAGGATAATAATGAAAATTATCAGGTGGGCTTAGCAGAGCTAA 3900
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3841 AACTCAACCAAAAGATTCAGGATAATAATGAAAATTATCAGGTGGGCTTAGCAGAGCTAA 3900

Qy       3901 GAACTTTAATGACAATTGAAAAAGATCAGCGTATTTCCGAGTTAATTAGTAGACATGAAG 3960
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3901 GAACTTTAATGACAATTGAAAAAGATCAGCGTATTTCCGAGTTAATTAGTAGACATGAAG 3960

Qy       3961 AAGAATCTAATATACTTAAAGCTGAATTAAACAAAGTAACATCTTTGCATAACCAAGCAT 4020
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3961 AAGAATCTAATATACTTAAAGCTGAATTAAACAAAGTAACATCTTTGCATAACCAAGCAT 4020

Qy       4021 TTGAAATAGAAAAAAACCTAAAAGAACAAATAATTGAACTGCAGAGTAAATTGGATTCAG 4080
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       4021 TTGAAATAGAAAAAAACCTAAAAGAACAAATAATTGAACTGCAGAGTAAATTGGATTCAG 4080

Qy       4081 AATTGAGTGCTCTTGAAAGACAAAAAGATGAAAAAATTACCCAACAAGAAGAGAAATACG 4140
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       4081 AATTGAGTGCTCTTGAAAGACAAAAAGATGAAAAAATTACCCAACAAGAAGAGAAATACG 4140

Qy       4141 AAGCTATTATCCAGAACCTTGAGAAAGACAGACAAAAATTGGTCAGCAGCCAGGAGCAAG 4200
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       4141 AAGCTATTATCCAGAACCTTGAGAAAGACAGACAAAAATTGGTCAGCAGCCAGGAGCAAG 4200

Qy       4201 ACAGAGAACAGTTAATTCAGAAGCTTAATTGTGAAAAAGATGAAGCTATTCAGACTGCCC 4260
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       4201 ACAGAGAACAGTTAATTCAGAAGCTTAATTGTGAAAAAGATGAAGCTATTCAGACTGCCC 4260

Qy       4261 TAAAAGAATTTAAATTGGAGAGAGAAGTTGTTGAGAAAGAGTTATTAGAAAAAGTTAAAC 4320
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       4261 TAAAAGAATTTAAATTGGAGAGAGAAGTTGTTGAGAAAGAGTTATTAGAAAAAGTTAAAC 4320

Qy       4321 ATCTTGAGAATCAAATAGCAAAAAGTCCTGCCATTGACTCTACCAGAGGAGATTCTTCAA 4380
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       4321 ATCTTGAGAATCAAATAGCAAAAAGTCCTGCCATTGACTCTACCAGAGGAGATTCTTCAA 4380
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Qy       4381 GCTTAGTTGCTGAACTTCAAGAAAAGCTTCAGGAAGAAAAAGCTAAGTTTCTAGAACAAC 4440
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       4381 GCTTAGTTGCTGAACTTCAAGAAAAGCTTCAGGAAGAAAAAGCTAAGTTTCTAGAACAAC 4440

Qy       4441 TTGAAGAGCAAGAAAAAAGAAAGAATGAAGAAATGCAAAATGTTCGAACATCTTTGATTG 4500
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       4441 TTGAAGAGCAAGAAAAAAGAAAGAATGAAGAAATGCAAAATGTTCGAACATCTTTGATTG 4500

Qy       4501 CGGAACAACAGACCAATTTTAACACTGTTTTAACAAGAGAGAAAATGAGAAAAGAAAACA 4560
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       4501 CGGAACAACAGACCAATTTTAACACTGTTTTAACAAGAGAGAAAATGAGAAAAGAAAACA 4560

Qy       4561 TAATAAATGATCTTAGTGATAAGTTGAAAAGTACAATGCAGCAACAAGAACGGGATAAAG 4620
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       4561 TAATAAATGATCTTAGTGATAAGTTGAAAAGTACAATGCAGCAACAAGAACGGGATAAAG 4620

Qy       4621 ATTTGATAGAGTCACTTTCTGAAGATCGAGCTCGTTTGCTTGAGGAAAAGAAAAAGCTTG 4680
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       4621 ATTTGATAGAGTCACTTTCTGAAGATCGAGCTCGTTTGCTTGAGGAAAAGAAAAAGCTTG 4680

Qy       4681 AAGAAGAAGTCAGTAAGTTGCGCAGTAGCAGTTTTGTTCCTTCACCATATGTAGCTACAG 4740
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       4681 AAGAAGAAGTCAGTAAGTTGCGCAGTAGCAGTTTTGTTCCTTCACCATATGTAGCTACAG 4740

Qy       4741 CCCCAGAACTTTATGGAGCTTGTGCACCTGAACTCCCAGGTGAATCAGATAGATCCGCTG 4800
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       4741 CCCCAGAACTTTATGGAGCTTGTGCACCTGAACTCCCAGGTGAATCAGATAGATCCGCTG 4800

Qy       4801 TGGAAACAGCAGATGAAGGAAGAGTGGATTCAGCAATGGAGACAAGCATGATGTCTGTAC 4860
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       4801 TGGAAACAGCAGATGAAGGAAGAGTGGATTCAGCAATGGAGACAAGCATGATGTCTGTAC 4860

Qy       4861 AAGAAAATATTCATATGTTGTCTGAAGAAAAACAGCGGATAATGCTGTTAGAACGAACAT 4920
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
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Qy       4921 TGCAATTGAAAGAAGAAGAAAATAAACGGTTAAATCAAAGACTGATGTCTCAGAGCATGT 4980
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Exhibit 2

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LOCUS       AB059622                6636 bp    mRNA    linear   PRI 11-OCT-2001.
DEFINITION  Homo sapiens RBICC mRNA for Rb1-inducible coiled coil protein,
            complete cds.
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ACCESSION AB059622

VERSION AB059622.1 GI:16040976

KEYWORDS .

SOURCE Homo sapiens (human)

ORGANISM Homo sapiens

Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.

REFERENCE 1 (bases 1 to 6636)

AUTHORS Chano,T., Kontani,K., Ikegawa,S., Okabe,H., Baldini,N. and Saeki,Y.

TITLE Cloning of a novel Rb1-inducible gene, RBICC

JOURNAL Unpublished

REFERENCE 2 (bases 1 to 6636)

AUTHORS Chano,T.

TITLE Direct Submission

JOURNAL Submitted (10-APR-2001) Tokuhiro Chano, Shiga University of Medical Science, Department of Clinical Laboratory Medicine; Seta, Tsukinowa, Otsu, Shiga 520-2192, Japan (E-mail:chano@belle.shiga-med.ac.jp, Tel:81-77-548-2600(ex.2600), Fax:81-77-548-2407)

FEATURES Location/Qualifiers

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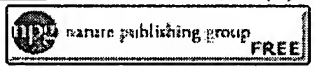
Exhibit 3

Oncogene. 2002 Feb 14;21(8):1295-8. Related Articles, Links



Identification of RB1CC1, a novel human gene that can induce RB1 in various human cells.

Chano T, Ikegawa S, Kontani K, Okabe H, Baldini N, Saeki Y.

Department of Basic Science for Health and Nursing, Shiga University of Medical Science,

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Multidrug resistance to anti-cancer agents (MDR) is a major barrier to successful cancer treatment. Current knowledge about genes that contribute to MDR is limited, however, and its mechanisms remain unclear. To identify genes involved in MDR, we performed differential display analysis and isolated a novel human gene, RB1CC1 (RBI-inducible Coiled-Coil 1). The 6.6-kb RB1CC1 cDNA encodes a putative 1594-amino-acid protein that contains a nuclear localization signal, a leucine zipper motif and a coiled-coil structure. Western blot analysis and immunocytochemical staining with anti-RB1CC1 antibody showed that endogenously expressed RB1CC1 protein localized to the nucleus. In MDR variants of human osteosarcoma cells, RB1CC1 expression increased in response to doxorubicin-induced cytotoxic stress and remained elevated for the duration of drug treatment. RB1CC1 expression levels correlated closely with those of RB1 (retinoblastoma 1) in cancer cell lines as well as in various normal human tissues. Moreover, introduction of wild-type RB1CC1 significantly induced RB1 expression in human leukemic cells. These data suggest that RB1CC1 may be a key regulator of RB1 gene expression.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 11850849 [PubMed - indexed for MEDLINE]

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APPLICATION NO. /CONTROL NO.	FILING DATE	FIRST NAMED INVENTOR / PATENT IN REEXAMINATION	ATTORNEY DOCKET NO.
10/516,558	01/25/2005	Tokuhiro Chano	3190-070

EXAMINER	
Peter Reddig, Ph.D.	
ART UNIT	**PAPER**
1642	

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below or on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

The specification discloses amino acid sequences without a respective sequence identifier, i.e. a SEQ ID NO: see p. 38, lines 24-26, Fig. 12, and Table 1. Hence, the disclosure fails to comply with the requirements of 37 CFR 1.821 through 1.825. In the absence of a sequence identifier for each sequence, Applicant must provide a computer readable form (CRF) copy of the sequence listing, an initial or substitute paper copy of the sequence listing, as well as any amendment directing its entry into the specification, and a statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by matter, as required by 37 CFR 1.821(e-f) or 1.825(b) or 1.825(d).

If a complete reply has not been submitted by the time period set in the accompanying Office action has expired, this application will become abandoned under 37 CFR 1.821(g).

Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a). In no case may an applicant extend the period for reply beyond the SIX MONTH statutory period. Direct the reply to the undersigned Applicant is requested to return a copy of the

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Please direct all replies to the United States Patent and Trademark Office via one (1) of the following:

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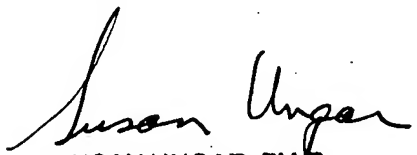
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter Reddig whose telephone number is 571-272-9031. The examiner can normally be reached on M-F 8:30 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Shanon Foley can be reached on 571-272-0898.

Peter Reddig, Ph.D.
Art Unit 1642



SUSAN UNGAR, PH.D
PRIMARY EXAMINER

Notice to Comply	Application No. 10/516,558	Applicant(s) Chano et al.	
	Examiner Peter Reddig	Art Unit 1642	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: The disclosure is lacking numerous sequence identifiers and sequence ID numbers, see the section titled "Sequence Listing" in the accompanying First Office Action on the Merits.

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", **as well as an amendment specifically directing its entry into the application**.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

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